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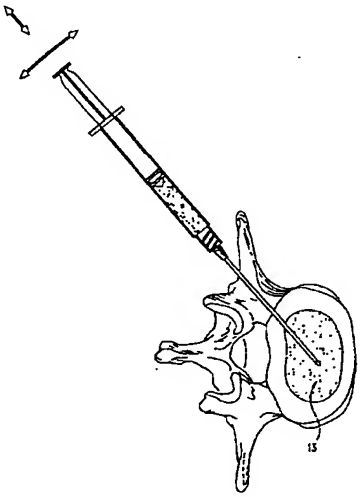

(57) Abstract: A method of augmenting an intervertebral disc nucleus by injecting or otherwise adding to a disc nucleus a plurality of particles of natural, collagen-rich tissue. The mean particle size of the pieces of natural, collagen-rich tissue may be between 0.25mm and 1.0mm. The particles may be dehydrated before implantation, and rehydrated after implantation, or they may be implanted in a "wet" state - such as a slurry or gel. Radiocontrast materials may be included to enhance imaging of the injected material. Other additives may include analgesics, antibiotics, proteoglycans, growth factors, stem cells, and/or other cells effective to promote healing and/or proper disc function.

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COMPOSITIONS AND METHODS FOR TREATING INTERVERTEBRAL DISCS WITH COLLAGEN-BASED MATERIALS

FIELD OF THE INVENTION

The present invention relates generally to materials and methods for augmenting intervertebral discs and/or synovial joints, and more particularly to materials and methods for augmenting intervertebral discs and/or synovial joints with collagen-based materials.

BACKGROUND OF THE INVENTION

A healthy intervertebral disc facilitates motion between pairs of vertebrae while absorbing and distributing shocks. The disc is composed o

f two parts: a soft central core (the nucleus pulposus) that bears the majority of the load, and a tough outer ring (the annulus fibrosis) that holds and stabilizes the core material.

As the natural aging process progresses, the disc may dehydrate and degenerate, adversely affecting its ability to adequately cushion and support the vertebral bodies. This natural desiccation, which in its more advanced state is often referred to as "black disc" because of the disc's dehydrated appearance on Magnetic Resonance Imaging [MRI], can cause discomfort to the patient as the vertebrae to come closer together – compressing the spinal nerves and causing pain. Even in a less advanced degenerative state, such as when the disc annulus is substantially sound, surgical treatments for augmenting, repairing, or replacing the disc and/or the disc nucleus are indicated.

Techniques for addressing degenerative disc disease have heretofore relied primarily on disc replacement methods. In cases in which a dehydrated and/or degenerating disc was augmented before disc replacement was required, the augmentation materials have primarily been synthetic devices that expand, are inflated, or deploy expanding elements when implanted into the disc.

Synovial joints are the most common joints of the mammalian appendicular skeleton, representing highly evolved, movable joints. A typical synovial joint comprises

two bone ends covered by layer of articular cartilage. The cartilage is smooth and resilient, and facilitates low-friction movement of the bones in the joint.

The bone ends and associated cartilage are surrounded by a joint capsule – a "sack" of membrane that produces synovial fluid. The capsule and fluid protect and support the cartilage and connective tissue, carrying nutrients to the articular cartilage and removing the metabolic wastes.

The articular cartilage is a thin (2-3mm) layer of hyaline cartilage on the epiphysis of the bone. It lacks a perichondrium, and thus has a limited capacity for repair when damaged. Additionally, the natural aging process can cause the articular cartilage to degenerate somewhat, reducing its capacity to protect and cushion the bone ends.

Zygapophysial joints, better known as facet joints, are the mechanism by which each vertebra of the spine connects to the vertebra above and/or below it. Each joint comprises two facet bones – an inferior facet and a superior facet – with the inferior facet of one vertebra connecting to the superior facet of an adjacent vertebra. The joints facilitate movement of the vertebra relative to each other, and allow the spine to bend and twist.

As in all synovial joints, where the facets contact each other there is a lining of cartilage lubricated by a thin layer of synovial fluid. The cartilage and synovial fluid decrease friction at the joint, extending joint life and preventing inflammation and associated pain.

As the natural aging process progresses, the cartilage covering the joint may deteriorate and start to fray. The fraying process may cause pieces of cartilage to break free, and the previously smooth surfaces may become rough. The facet bones then begin to rub together, creating friction which leads to further deterioration of the joint. Moreover, the nerves associated with the joint become irritated and inflamed, causing severe pain and restricting movement of the spine.

Techniques for addressing degeneration of synovial joints in general, and facet joints in particular, joint have heretofore relied primarily on injections to block pain and reduce inflammation. This treatment is only temporary though, and rarely leads to any significant improvement of the underlying condition.

A need therefore exists for materials and methods effective for augmenting intervertebral discs and/or synovial joints with natural materials. The present invention addresses those needs.

SUMMARY OF THE INVENTION

Briefly describing one aspect of the present invention, there is provided a method of augmenting an intervertebral disc nucleus by injecting or otherwise adding to the disc nucleus a plurality of particles of natural, collagen-rich tissue. The mean particle size of the pieces of natural, collagen-rich tissue may be between 0.25mm and 1.0mm. The particles may be dehydrated before implantation, and rehydrated after implantation, or they may be implanted in a "wet" state – such as a slurry or gel. Radiocontrast materials may be included to enhance imaging of the injected material. Other additives may include analgesics, antibiotics, proteoglycans, growth factors, stem cells, and/or other cells effective to promote healing and/or proper disc function.

Objects and advantages of the claimed invention will be apparent from the following description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-1D show a procedure for injecting a collagen-based material into an intervertebral disc, according to one preferred embodiment of the present invention.

FIGS. 2A-2F show a procedure for injecting a collagen-based material into an intervertebral disc, according to another preferred embodiment of the present invention.

FIGS. 3A-1D show a procedure for injecting a collagen-based material into a facet joint, according to one preferred embodiment of the present invention.

FIGS. 4A-2F show a procedure for injecting a collagen-based material into a facet joint, according to another preferred embodiment of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

For the purposes of promoting an understanding of the principles of the invention, reference will now be made to certain preferred embodiments and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and further modifications in the preferred embodiments being contemplated as would normally occur to one skilled in the art to which the invention relates.

As indicated above, one aspect of the present invention relates to materials and methods for using collagen-based material to treat a degenerating intervertebral disc or synovial joint. In the most preferred embodiments the collagen-based material is injected into the disc or the joint capsule. In some preferred embodiments the inventive method includes surgically adding to an intervertebral disc or a synovial joint a composition comprising particulate collagen-based material. In other embodiments the inventive method includes surgically adding to a disc or synovial joint a composition consisting essentially of particulate collagen-based material. The collagen-based material may be injected into a disc nucleus that is contained in a substantially sound annulus, or it may be injected into a disc nucleus that is contained in a damaged or defective annulus.

The collagen-based material may be derived from natural, collagen-rich tissue, such as intervertebral disc, fascia, ligament, tendon, demineralized bone matrix, etc. The material may be autogenic (autograft), allogenic (allograft), or xenogenic (xenograft), or it may be of human-recombinant origin. In alternative embodiments the collagen-based material may be a synthetic, collagen-based material. Examples of preferred collagen-rich tissues include disc annulus, fascia lata, planar fascia, anterior or posterior cruciate ligaments, patella tendon, hamstring tendons, quadriceps tendons, Achilles tendons, skins, and other connective tissues.

The collagen-based material may be provided in any form appropriate for introduction into a disc space or a synovial joint. For example, the material may be a solid, porous, woven, or non-woven material, and may be provided as particles, small pieces, gel, solution, suspension, paste, fibrous material, etc. The material may be used while it is still fresh and hydrated, or it may be used after having been processed, such as having been frozen and/or dehydrated.

In some embodiments the material is provided in a dehydrated state, and is "rehydrated" after injection in the joint. In other embodiments the material is implanted in a hydrated state. When the material is implanted in a hydrated state, it may be that way because it has never been dehydrated, or it may have been dehydrated and reconstituted. When reconstituted, the material may be reconstituted with saline or another aqueous medium, or it may be reconstituted with a non-aqueous medium such as ethylene glycol or another alcohol. Moreover, when provided in a "hydrated" state, the material may be provided as a gel, solution, suspension, dispersion, emulsion, paste, etc.

In the most preferred embodiments the material is a particulate and/or fibrous material suitable for injection through a hypodermic needle into a disc or synovial joint.

In the most preferred embodiments the collagen material is provided as particles ranging between .05mm and 5mm in size, or more preferably between .05mm and 1.0mm in size. When materials such as fascia lata or disc annulus particles are used the particles preferably range in size from .05mm to 5mm, or more preferably between .10mm and 1.0mm. When materials such as demineralized bone matrix or gelatin are used the particles preferably range in size from .05mm to 3mm. When small plugs of material are used the plugs preferably range in size from .5mm to 5mm. In some embodiments larger sized pieces, such as pieces up to 20mm in size, may be used. For the purposes of this description, the particle size is the largest dimension of a particle. Thus, a particle having a length of 1.0mm, a width of 0.25mm, and a height of 0.50mm would have a "particle size" of 1.0mm.

In some embodiments a natural, collagen-rich tissue having a mean particle size of between 0.25mm and 1.0mm is used. The mean particle size is the average particle size of the particles used in the treatment, i.e., when the particle size of each particle of collagen-rich material used in the treatment is considered, the mean particle size is the average of those sizes. In some alternative embodiments, a natural, collagen-rich tissue having a mean particle size of between 0.25mm and 0.5mm is used, while in other alternative embodiments a natural, collagen-rich tissue having a mean particle size of between 0.50mm and 1.0mm is used.

The materials may be processed or fabricated using more than one type of tissue. For example, mixtures of fascia lata and demineralized bone matrix may be preferred in appropriate cases, as may mixtures of DBM and annulus fibrosis material.

Cross-linking agents may be added to the formulation to promote cross-linking of the collagen material. For example, glutaraldehyde or other protein cross-linking agents may be included in the formulation. The cross-linking agents may promote covalent or non-covalent crosslinks between collagen molecules. Similarly, agents to inhibit protein denaturization may also be included. Crosslinking agents that would be appropriate for use in the claimed invention are known to persons skilled in the art, and may be selected without undue experimentation.

When the material is to be used as a slurry or gel, additives to promote slurry or gel formation may also be included. These additives may promote protein folding, water binding, protein-protein interactions, and water immobilization.

In addition, a radiographic contrast media, such as barium sulfate, or a radiocontrast dye, such as sodium diatrizoate (HYPAQUE®), may be included to aid the surgeon in tracking the movement and/or location of the injected material. Radiocontrast materials appropriate for use in discography are known to persons skilled in the art, and may be selected for use in the present invention without undue experimentation.

Finally, other additives to provide benefits to the injected collagen-based material may also be included. For example, pharmacological agents such as growth factors that may advantageously repair the endplates and/or the annulus fibrosis may be included. The growth factor may include a bone morphogenetic protein, transforming growth factor-β (TGF-β), insulin-like growth factor, platelet-derived growth factor, fibroblast growth factor or other similar growth factor or combination thereof having the ability to repair the endplates and/or the annulus fibrosis of an intervertebral disc.

The growth factors are typically included in the implants in therapeutically effective amounts. For example, the growth factors may be included in the implants in amounts effective in repairing an intervertebral disc, including repairing the endplates and the annulus fibrosis. Such amounts will depend on the specific case, and may thus be determined by the skilled artisan, but such amounts may typically include less than about 1% by weight of the growth factor. The growth factors may be purchased commercially or may be produced by methods known to the art. For example, the growth factors may be produced by recombinant DNA technology, and may preferably be derived from humans. As an example, recombinant human bone morphogenetic proteins (rhBMPs), including rhBMP 2-14, and especially rhBMP-2, rhBMP-7, rhBMP-12, rhBMP-13, and heterodimers thereof may be used. However, any bone morphogenetic protein is contemplated including bone morphogenetic proteins designated as BMP-1 through BMP-18.

BMPs are available from Genetics Institute, Inc., Cambridge, Massachusetts and may also be prepared by one skilled in the art as described in U.S. Patent Nos. 5,187,076 to Wozney et al.; 5,366,875 to Wozney et al.; 4,877,864 to Wang et al.; 5,108,922 to Wang et al.; 5,116,738 to Wang et al.; 5,013,649 to Wang et al.; 5,106,748 to Wozney et al.; and PCT Patent Nos. WO93/00432 to Wozney et al.; WO94/26893 to Celeste et al.;

and WO94/26892 to Celeste et al. All bone morphogenic proteins are contemplated whether obtained as above or isolated from bone. Methods for isolating bone morphogenetic protein from bone are described, for example, in U.S. Patent No. 4,294,753 to Urist and Urist et al., 81 PNAS 371, 1984.

In other forms of the invention, the pharmacological agent may be one used for treating various spinal conditions, including degenerative disc disease, spinal arthritis, spinal infection, spinal tumor and osteoporosis. Such agents include antibiotics, analgesics, anti-inflammatory drugs, including steroids, and combinations thereof. Other such agents are well known to the skilled artisan. These agents are also used in therapeutically effective amounts. Such amounts may be determined by the skilled artisan depending on the specific case.

The pharmacological agents are preferably dispersed within the collagen-based material for *in vivo* release. The pharmacological agents may be dispersed in the material by soaking the material in an appropriate solution containing the agent, or by other appropriate methods known to the skilled artisan. In other forms of the invention, the pharmacological agents may be chemically or otherwise associated with the material. For example, the agents may be included in the fluid phase in which the collagen-based material is suspended or otherwise dispersed.

Polysaccharides such as proteoglycans and/or hyaluronic acid may also be included to attract and/or bind water to keep the disc or synovial joint hydrated. Additionally, growth factors and/or other cells (e.g., intervertebral disc cells, stem cells, etc.) to promote healing, repair, regeneration and/or restoration of the joint, and/or to facilitate proper joint function, may also be included. Additives appropriate for use in the claimed invention are known to persons skilled in the art, and may be selected without undue experimentation.

In some embodiments the collagen material is dehydrated before injection into the disc or joint, where it is rehydrated by absorbing fluid from the surrounding area. In other embodiments the collagen material is provided as a gel, slurry, or other hydrated formulation before implantation.

The collagen-based material is "surgically added" to the intervertebral disc or the synovial joint. That is, the material is added by the intervention of medical personnel, as distinguished from being "added" by the body's natural growth or regeneration processes. The surgical procedure preferably includes injection through a hypodermic needle,

although other surgical methods of introducing the collagen-based material into the disc or joint may be used. For example, the material may be introduced into a disc or synovial joint by extrusion with an extruder through a dilated opening, infusion through a catheter, insertion through an opening created by trauma or surgical incision, or by other means of invasive or minimally invasive deposition of the materials into the disc or joint space.

When the collagen-based material is combined with another biologically active substance, the two materials may be added to the disc nucleus together or separately. For example, the two materials may be added simultaneously by mixing the materials together and then adding them with a single barrel syringe, or by leaving the materials unmixed in a double barrel syringe and using a mixing tip to simultaneously inject the two materials. Alternatively, the two materials may be added sequentially using a hypodermic needle or other means of implanting the material.

Referring now to the drawings, FIGS. 1A-1D show one method of injecting a collagen-based material into a disc. In FIG. 1A, dehydrated particulate fascia lata or annulus fibrosis material 11 is provided in a syringe 12 (in a sterile package). The material is rehydrated and/or dispersed in a suspension medium as shown in FIG. 1B, to provide a wet dispersion 13 of collagen-based material. A hypodermic needle 14 is attached to syringe 12, and the syringe is inserted into a nucleus pulposus 15 contained within a disc annulus 16 (FIG. 1C). The needle/syringe may be moved around within the disc space, sweeping from side to side and back and forth, to ensure uniform distribution of the collagen-based material 13 within the disc space, as shown in FIG. 1D. It is preferred, however, that the tip of the needle be maintained near the center of the disc to ensure deposition of the material within the nuclear disc space, and to minimize potential leakage.

Alternatively, small collagen plugs 21 may be inserted into the disc space as shown in FIGS. 2A-2F. The collagen plugs 21 may be compressed before or by insertion into a small diameter tube 22, and are provided in a delivery cannula 23 (FIGS. 2A-2C). The delivery cannula 23 is attached to a dilator 24.

The compressed plugs are inserted into a disc nucleus 25 having a substantially intact annulus 26 by penetrating the annulus with a guide needle 27 (FIG. 2D). Dilator 24, preferably with delivery cannula 23 already attached, is inserted through the annulus over guide needle 27 (FIG. 2E). The collagen plugs 21 are then ready for injection (or extrusion) into the disc space.

The collagen plugs are deposited into the disc space. As with the wet particulate/fibrous material, the cannula may be moved up and back, and/or side to side, to ensure even distribution of the plugs (FIG. 2F) a plunger 28 may be used to push the plugs from the cannula.

The plugs expand upon exiting the dilator, and may further expand as they rehydrate in the disc space.

Benefits and advantages arising from use of the materials and methods of the present invention may include:

(1) the invention provides lubrication and/or cushioning to degenerated synovial joints, improving or restoring proper joint function;

(2) the rehydration provided by the invention is expected to slow the degenerative process;

(3) the invention relieves pain due to improved lubrication of the joint;

(4) the procedure is percutaneous or a minimally invasive outpatient procedure;

(5) the risks are minimal, as similar techniques and materials are used in cosmetic procedures;

(6) the materials are biocompatible since natural or human-recombinant collagen-based materials are used;

As previously indicated, in other preferred embodiments the materials and methods of the present invention may be used to treat synovial joints in the spine, particularly facet joints. In other preferred embodiments hip, knee, ankle, finger, toe, elbow, shoulder, wrist, sacroiliac, temporomandibular, carpometacarpal, etc., joints may all be treated by injecting a collagen-source material into the joint space to supplement/augment the cartilage that lubricates the joint. Advantages commensurate with those identified above may be obtained by the use of such alternative embodiments.

Reference will now be made to specific examples using the processes described above. It is to be understood that the examples are provided to more completely describe preferred embodiments, and that no limitation to the scope of the invention is intended thereby.

EXAMPLE 1A

Hydrated Particulate Fascia Lata

A suspension of particulate or fibrous (autologous or allogenic) fascia lata is prepared in a biocompatible medium such as saline or ethylene glycol. The particle size ranges from 0.1 mm to 5 mm, with most particles being between 0.25 and 2 mm.

The suspension is injected directly into the nuclear disc space through an intact annulus using a hypodermic needle, and is contained within the disc space following injection. The medium subsequently diffuses out of the disc space and leaves the fascia lata material behind.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained with a single injection of material. Alternatively, several smaller doses/injections may be used to achieve comparable results.

EXAMPLE 1B

Hydrated Particulate Fascia Lata With Crosslinking Agent

A suspension of particulate or fibrous (autologous or allogenic) fascia lata is prepared in a biocompatible medium such as saline or ethylene glycol. The particle size ranges from 0.1 mm to 5 mm, with most particles being between 0.25 mm and 2 mm. A glutaraldehyde crosslinking agent is added to promote collagen crosslinking.

The suspension is injected directly into the nuclear disc space through an intact annulus using a hypodermic needle, and is contained within the disc space following injection. The medium subsequently diffuses out of the disc space and leaves the fascia lata material behind.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLE 1C

Dehydrated Particulate Fascia Lata

Dehydrated fascia lata material is provided in particulate form. Particle sizes range between 0.05 mm and 3 mm, with most particles being between 0.10 mm and 1 mm. The dehydrated material is loaded in a specially designed syringe for delivery of solid materials.

The material is extruded into the nuclear disc space of the treated disc through a small dilated annular opening. The material remains inside the disc space after the needle is removed. It subsequently absorbs moisture or body fluids and swells up in vivo.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLE 2A

Hydrated Particulate Disc Annulus Material

A suspension of particulate or fibrous allogenic annulus fibrosis is prepared in a biocompatible medium such as saline or ethylene glycol. The particle size ranges from 0.1 mm to 5 mm, with most particles being between 0.25 and 2 mm.

The suspension is injected directly into the nuclear disc space through an intact annulus using a hypodermic needle. The suspension is contained within the disc space following injection. The medium subsequently diffuses out of the disc space and leaves the annulus fibrosis material behind.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLE 2B

Hydrated Particulate Disc Annulus Material With Crosslinking Agent

A suspension of particulate or fibrous allogenic annulus fibrosis is prepared in a biocompatible medium such as saline or ethylene glycol. The particle size ranges from 0.1 mm to 5 mm, with most particles being between 0.25 and 2 mm. A glutaraldehyde crosslinking agent is added to promote collagen crosslinking.

The suspension is injected directly into the nuclear disc space through an intact annulus using a hypodermic needle. The suspension is contained within the disc space following injection. The medium subsequently diffuses out of the disc space and leaves the annulus fibrosis material behind.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLES 3A-3C

Dehydrated Annulus Fibrosis

Dehydrated annulus fibrosis is provided in granule, particulate and powder form, for example 3A-3C respectively. Particle sizes range between 0.05 mm and 3 mm, with most particles being between 0.10 mm and 1 mm. The dehydrated material is loaded in a specially designed syringe for delivery of solid materials.

The material is extruded into the nuclear disc space of the treated disc through a small dilated annular opening. The material remains inside the disc space after the needle is removed. It subsequently absorbs moisture or body fluids and swells up in vivo.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLES 4A-4B

Demineralized Bone Matrix (DBM) Gel

Demineralized bone matrix (DBM) gel is provided with and without glutaraldehyde as a cross-linker additive (examples 4A and 4B, respectively). In both cases the material is warmed up to an appropriate temperature for melting or thinning out the gel, and is injected directly into the nuclear disc space through an intact annulus using a hypodermic needle. The DBM gel becomes solidified in the disc space after injection.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLES 4C

Dehydrated Demineralized Bone Matrix (DBM)

Dehydrated DBM is provided in granule, particulate and powder form. Particle sizes range between 0.05 mm and 3 mm, with most particles being between 0.10 mm and 1 mm. The dehydrated material is loaded in a specially designed syringe for delivery of solid materials.

The material is extruded into the nuclear disc space of the treated disc through a small dilated annular opening. The material remains inside the disc space after the needle is removed. It subsequently absorbs moisture or body fluids and swells up in vivo.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLE 5A-5D

Mixtures of annulus fibrosis and demineralized bone matrix

Mixtures of particulate and fibrous allogenic annulus fibrosis and demineralized bone matrix (DBM) gel, with and without additives and/or cross-linkers, are provided. The materials are warmed up to an appropriate temperature for melting or thinning out the gel mixture, and are injected directly into the nuclear disc space through an intact annulus using a hypodermic needle. The gel mixture becomes solidified in the disc space after injection.

Inspection of the disc reveals that an appropriate level of augmentation may be obtained through either a single injection of material, or by multiple injections.

EXAMPLE 6

Elongated cylindrical plugs (0.5 mm to 5 mm in diameter, preferably 1 mm to 2 mm) of solid, porous, or fibrous collagen are provided in a dehydrated state. The plugs are compressed in the radial direction and are inserted into delivery cannula for delivery into disc space.

A guide wire or needle is used to penetrate the disc space through an intact annulus. A dilator is subsequently inserted into the disc space over the guide wire/needle, and the guide wire/needle is removed. The delivery cannula containing a collagen plug is attached to the dilator prior to extrusion of the plug into the disc space. As the plugs absorb moisture after entering the disc space, they become more compliant, flexible and expanded.

The level of disc augmentation achieved depends on the number of plugs inserted, and/or on the total plug volume deposited in the disc space.

EXAMPLE 7

Cylindrical plugs or rolls (2 mm – 20 mm in diameter, preferably 10 – 15 mm) of solid, porous, or fibrous collagen are provided in a dehydrated state. The dehydrated plugs are typically more rigid than those in hydrated state, and thus, can be easily inserted into the disc space through an annular opening created by trauma or surgical incision.

Nucleotomy is necessary before the plug can be inserted. As the plugs absorb moisture after entering the disc space, they become more compliant, flexible and expanded.

The level of disc augmentation/replacement achieved depends on the size and number of plugs inserted into the disc space.

EXAMPLE 8

Particulate fascia used for cosmetic procedure (FASCIAN®) was modified to include a radiocontrast media. A small quantity of barium sulfate powder was blended with 80 mg of >0.5 mm Gastrocemius Fascia for visualization under fluoroscopic imaging. About 1-1.5 cc of water was added to the blend in the syringe for hydration.

After hydration for 5-10 minutes, the material (Fascian/Barium Sulfate/Water or F.B.W.) was injected into the nuclear disc space of a harvested porcine intervertebral disc. X-ray images of the disc were obtained before and after injection.

A small increase in disc height was noticed after injection. Also, manual compression indicated that the disc was stiffer after injection. The injected disc was also tested under compression up to 5000N. There was no gross leakage observed during the compression test. Only a slight oozing of a small amount of injected material was observed at the injection site, but it stopped quickly.

The disc was cut in the horizontal plane to confirm the location of the injected material. F.B.W. was found contained within the disc annulus and mixed in with nucleus pulposus.

EXAMPLE 9

Particulate fascia used for cosmetic procedures (FASCIAN®) was modified before experimentation to include a radiocontrast material. A small quantity of radio-contrast dye

or barium sulfate powder was blended with about 200 mg of 0.25 – 1.0 mm Gastrocemius Fascia for visualization under fluoroscopic imaging. About 1.5-3 cc of saline was added to the blend in the syringe for hydration.

After hydration for about 30 minutes, the material (Fascian/Dye or Barium Sulfate/Water) was injected into the nuclear disc space of cadaveric intervertebral discs (L2-3 and L3-4). X-ray images of the discs were obtained before and after injection. A small increase in disc height was noticed radiographically after injection. There was no gross leakage observed at the injection site. In the case of L3-4 injection, the needle tip was maintained approximately at the center of the disc, which resulted in material deposition mainly within the nucleus pulposus.

EXAMPLE 10

Particulate fascia (FASCIAN®) having particle sizes of 0.25mm and 0.5mm was purchased from Fascia BioSystems. Collagen solutions were prepared, with each solution consisting of approximately 80 mg of particulate fascia, 0.75 ml of saline, and 0.25 ml HYPAQUE® radiocontrast solution.

Thoracic and lumbar discs in two pigs were subjected to stabbing injury. The injured discs were then injected with 1-2 ml of collagen solution at 4 weeks after injury. The injections were performed using a 3 ml syringe, a 20 gauge hypodermic needle and a graft placement device. Confirming X-ray was taken using C-arm fluoroscopy.

The injured discs appeared to have somewhat reduced heights at four weeks after injury. Of approximately 12 injected discs, only one leakage was observed. The amount of leakage was estimated to be less than 20% of the total volume injected. The low incidence of leakage indicates that the annulus is capable of self-sealing when a small gauge needle is used for injection.

The disc height increased upon collagen injection depending on the injected volume. In particular, an approximately 46% increase in disc height was achieved with 2 ml injection. In some cases the disc height gain was reduced after injection as radio-contrast dye and water molecules diffused out of the disc under intra-discal pressure.

While the invention has been illustrated and described in detail in the drawings and foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiment has been shown and

described and that all changes and modifications that come within the spirit of the invention are desired to be protected.

CLAIMS

What is claimed is:

1. A method of augmenting intervertebral disc nucleus, said method comprising surgically adding to an intervertebral disc nucleus contained within a disc annulus:

a) a plurality of particles of natural, collagen-rich tissue, wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.05mm and 5.0mm; and

b) a biologically active substance effective to promote healing, repair, regeneration and/or restoration of the disc, and/or to facilitate proper disc function.

2. The method of claim 1 wherein said biologically active substance is a growth factor.

3. The method of claim 2 wherein said growth factor comprises one or more members selected from the group consisting of bone morphogenetic protein, transforming growth factor-β (TGF-β), insulin-like growth factor, platelet-derived growth factor, fibroblast growth factor, or other growth factors having the ability to repair the endplates and/or the annulus fibrosis of an intervertebral disc.

4. The method of claim 1 wherein said biologically active substance comprises one or more members selected from the group consisting of antibiotics, analgesics, anti-inflammatories, and steroids.

5. The method of claim 1 wherein said biologically active substance comprises stem cells.

6. The method of claim 1 wherein said method further includes adding a radiographic contrast media to the intervertebral disc nucleus.

7. The method of claim 1 wherein said method further includes adding a polysaccharide to the intervertebral disc nucleus.

8. The method of claim 7 wherein said polysaccharide is a proteoglycan and/or a hyaluronic acid.

9. The method of claim 1 wherein said method further includes adding a cross-linking agent to the intervertebral disc nucleus, to promote crosslinking of collagen molecules.

10. The method of claim 1 wherein said biologically active substance is effective for treating one or more medical conditions selected from the group consisting of degenerative disc disease, spinal arthritis, spinal infection, spinal tumor, and osteoporosis.

11. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.25mm and 1.0mm.

12. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.25mm and 0.5mm.

13. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.5mm and 1.0mm.

14. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue are added to the disc nucleus in a dehydrated state.

15. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue are added to the disc nucleus in a non-dehydrated state.

16. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue are added to the disc nucleus as a gel.

17. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue are added to the disc nucleus as a suspension.

18. The method of claim 1 wherein said natural, collagen-rich tissue is an allograft tissue.

19. The method of claim 1 wherein said natural, collagen-rich tissue is an autograft tissue.

20. The method of claim 1 wherein said natural, collagen-rich tissue is a xenograft tissue.

21. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue, and said biologically active substance are surgically added simultaneously.

22. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue, and said biologically active substance are surgically added sequentially.

23. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue, and said biologically active substance are surgically added by needle injection.

24. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue, and said biologically active substance are surgically added by catheter infusion.

25. The method of claim 1 wherein said plurality of particles of natural, collagen-rich tissue, and said biologically active substance are surgically added by extrusion.

26. A kit for augmenting an intervertebral disc nucleus, said kit comprising:

a) a plurality of particles of natural, collagen-rich tissue, wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.05mm and 5.0mm; and

b) a biologically active substance effective to promote healing, repair, regeneration and/or restoration of the disc, and/or to facilitate proper disc function.

27. An augmented intervertebral disc, comprising:

a) a disc annulus fibrosis;

b) a surgically-added plurality of particles of natural, collagen-rich tissue, wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.05mm and 5.0mm; and

c) a surgically-added biologically active substance effective to promote healing, repair, regeneration and/or restoration of the disc, and/or to facilitate proper disc function.

28. A composition effective for augmenting intervertebral disc nucleus, said composition comprising:

a) a plurality of particles of natural, collagen-rich tissue, wherein said plurality of particles of natural, collagen-rich tissue has a mean particle size of between 0.05mm and 5.0mm; and

b) a biologically active substance effective to promote healing, repair, regeneration and/or restoration of the disc, and/or to facilitate proper disc function.

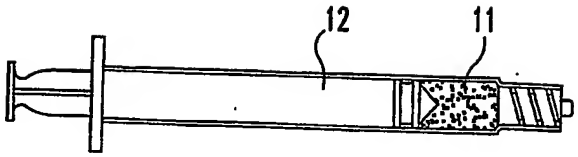

Fig. 1A

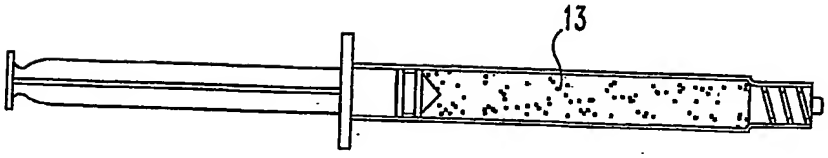

Fig. 1B

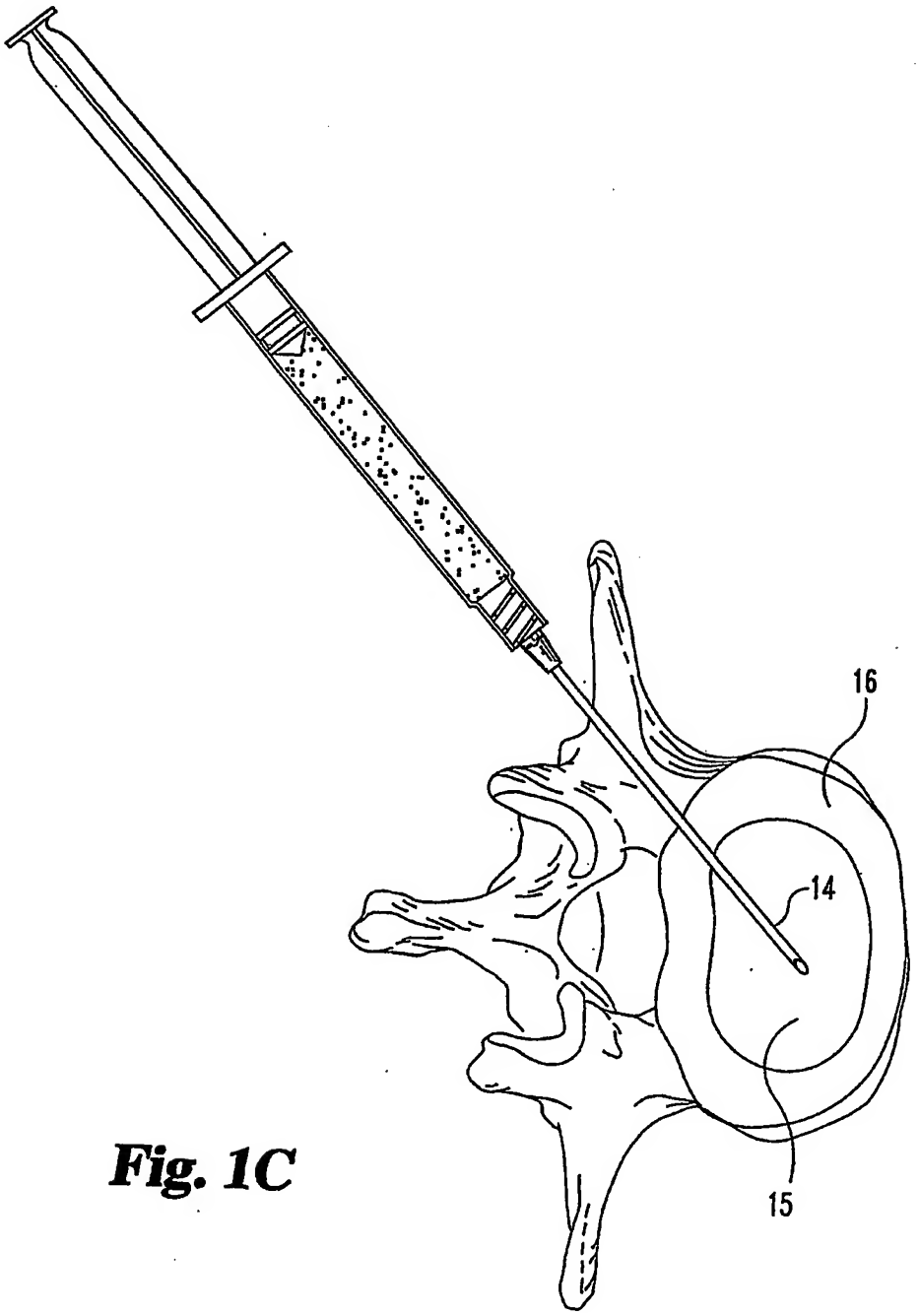

Fig. 1C

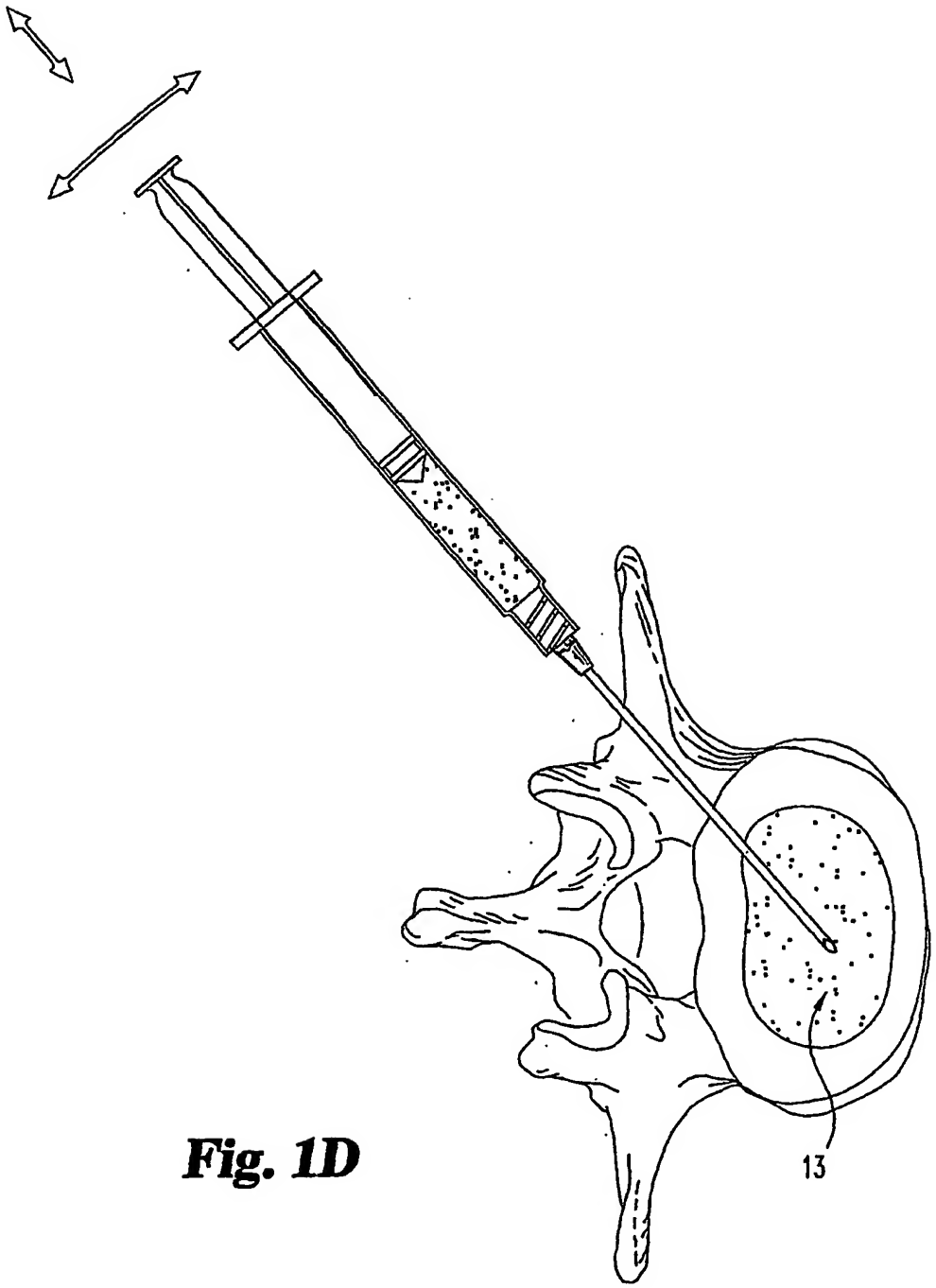

Fig. 1D

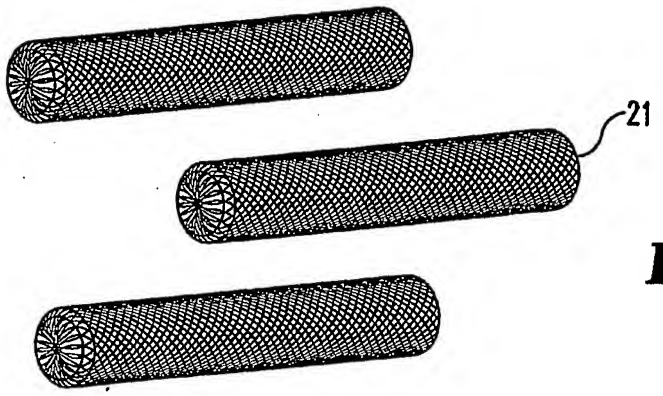

Fig. 2A

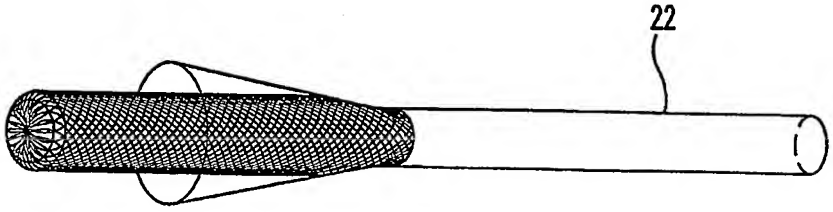

Fig. 2B

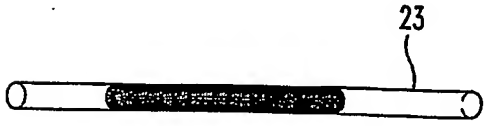

Fig. 2C

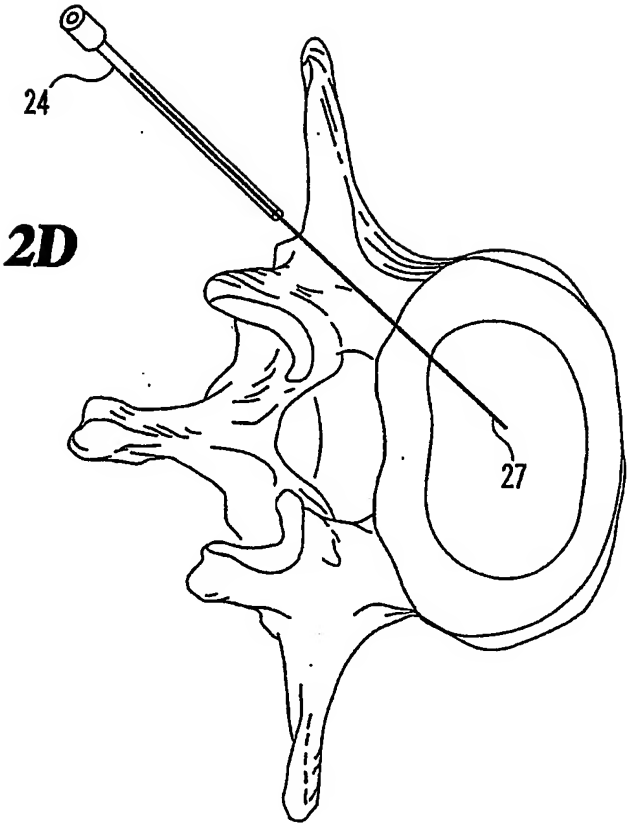

Fig. 2D

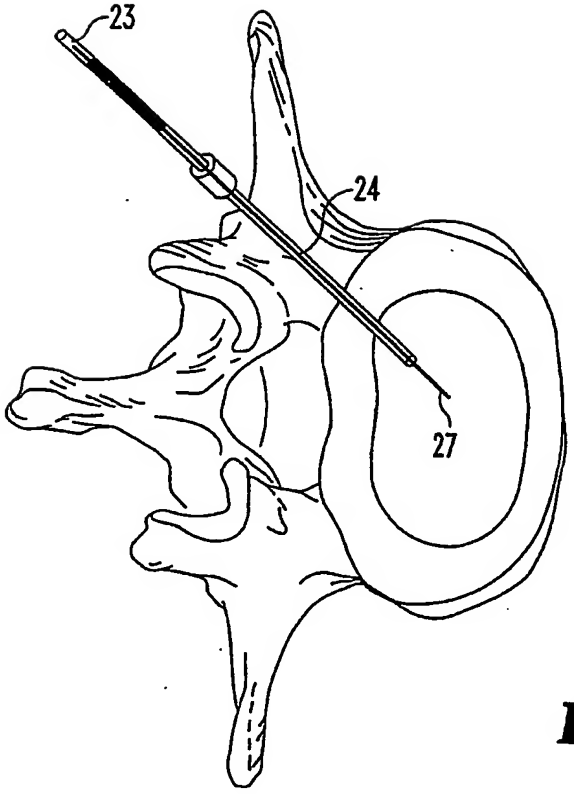

Fig. 2E

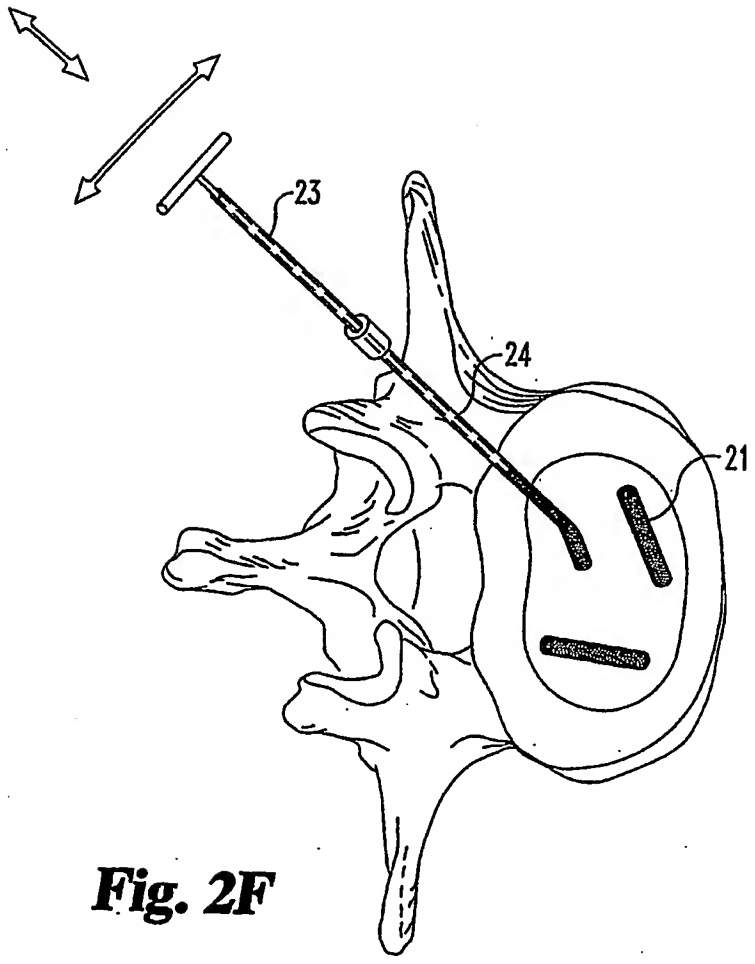

Fig. 2F

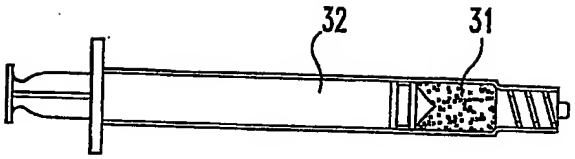

Fig. 3A

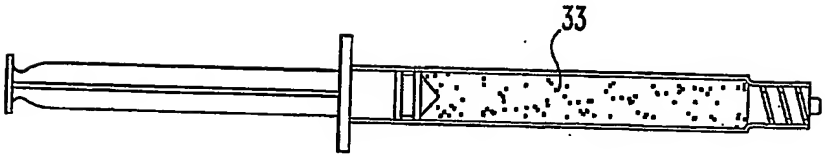

Fig. 3B

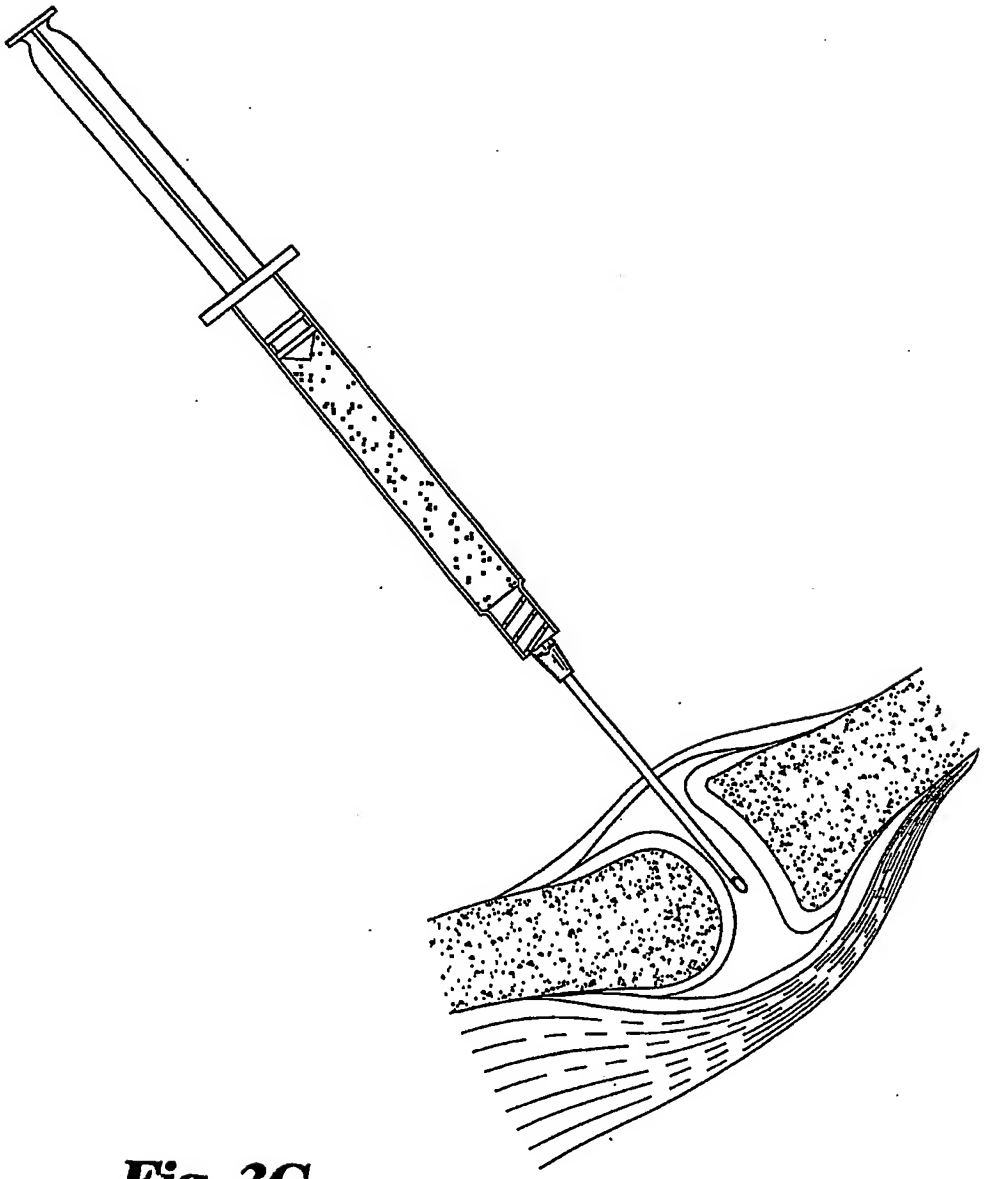

Fig. 3C

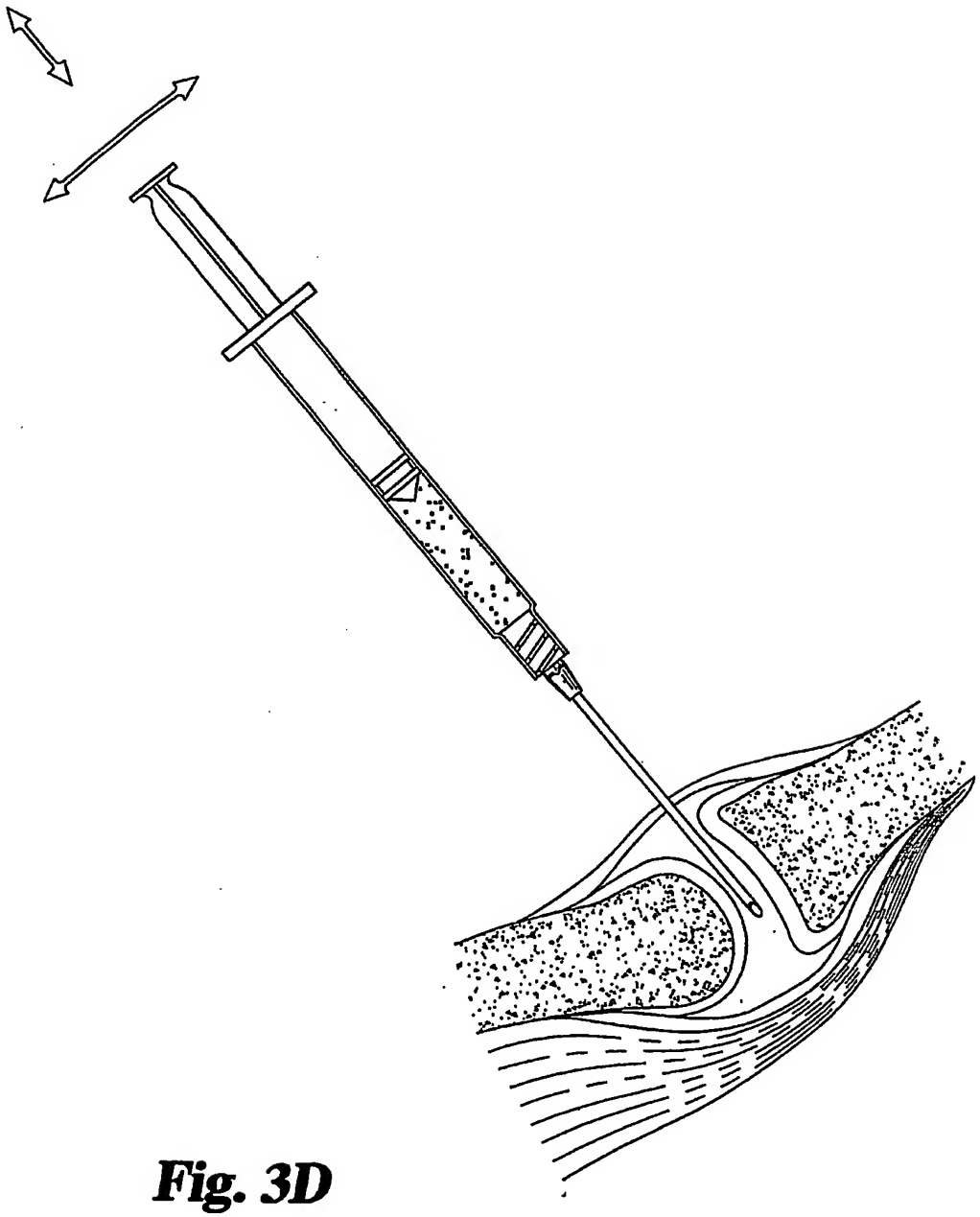

Fig. 3D

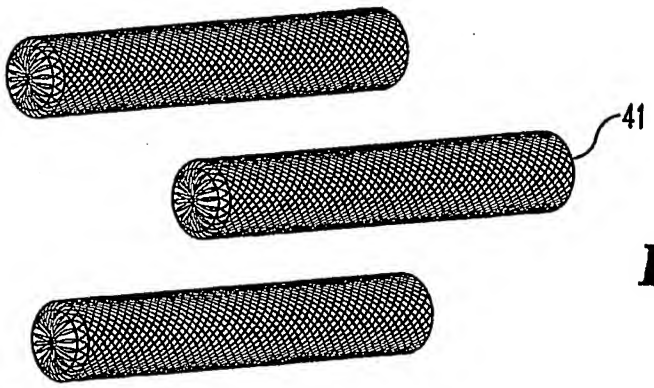

Fig. 4A

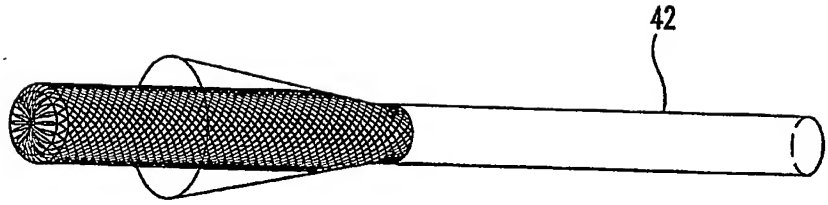

Fig. 4B

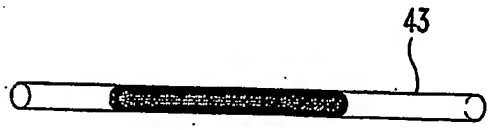

Fig. 4C

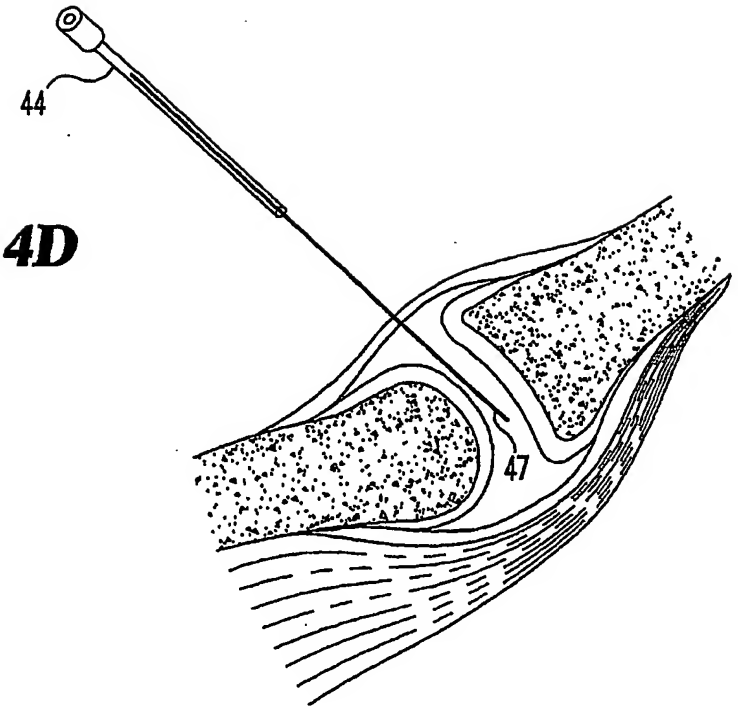

Fig. 4D

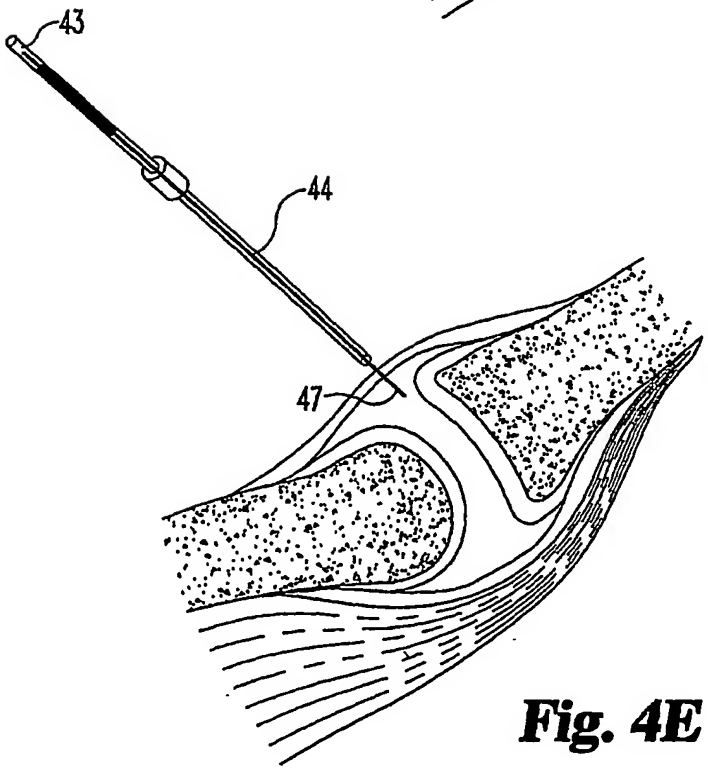

Fig. 4E

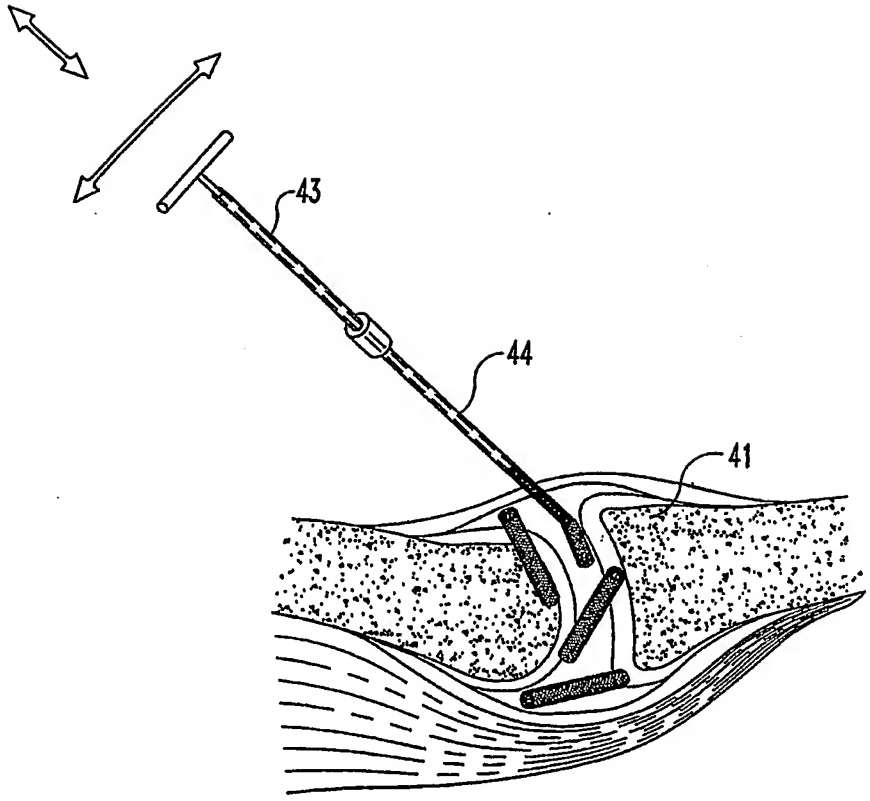

Fig. 4F

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/000581

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/44 A61L27/50 A61B17/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/026189 A (SDGI HOLDINGS) 1 April 2004 (2004-04-01) abstract; claims 1-3,16-18; examples 5A-5D page 2, line 24 - page 3, line 30 page 4, line 16 - line 28	26-28
X	WO 2004/093934 A (SDGI HOLDINGS) 4 November 2004 (2004-11-04) page 11, line 17 - line 29 page 12, line 29 - page 14, line 32	26-28
X	WO 2004/045667 A (SDGI HOLDINGS) 3 June 2004 (2004-06-03) abstract; claims 1-3,21-23 page 3, line 17 - page 4, line 26 page 5, line 11 - line 19	26-28

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2006	15/05/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nice, P

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/000581

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2005/119754 A1 (TRIEU H.H.) 2 June 2005 (2005-06-02) claim 1	26-28
P,X	US 2005/118228 A1 (TRIEU H.H.) 2 June 2005 (2005-06-02) claims 1-8	26-28
P,X	US 2005/197707 A1 (TRIEU H.H. & SHERMAN M.C.) 8 September 2005 (2005-09-08) claims 1,3,17	26-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/000581

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-25
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/000581

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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